Acute Lymphoblastic Leukemia in Children: Nonrandomized Comparison of Conventional vs. Intensive Chemotherapy at the National Cancer Institute of Colombia

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Background. This study aimed to compare the therapeutic efficacy of two treatments for childhood acute lymphoblastic leukemia (ALL), and to evaluate the feasibility of intensive chemotherapy in a developing country.

Methods. The study was conducted at the National Cancer Institute in Bogota, Colombia. Untreated ALL patients under 16 years of age were divided into two groups: a historical control cohort (HC) of 141 patients treated with conventional chemotherapy and an intensive chemotherapy cohort (IC) of 130 patients treated with a modified Berlin-Frankfurt-Munster protocol (m-BFM). Patients were clinically classified into risk categories for relapse, and followed through July 31, 1995. Disease-free survival (DFS) curves were obtained using the Kaplan-Meier method and were compared by the log rank test.

Results. Therapy groups had similar clinical baseline characteristics. Nonresponse rate to induction was higher in the HC group (16.3%) than in the IC cohort (7.6%) ($P = 0.047$), but deaths during induction were more frequent among m-BFM patients (13.8%) than in the HC group (6.4%) ($P = 0.064$). Bone marrow relapses after complete remission were less common in the IC group than in the HC group (19.4% and 45.9%, respectively; $P = 0.0001$), but central nervous system relapses showed no difference (12.8% in the HC and 16.3% under IC; $P = 0.6$). The DFS rates at 10 years were higher for the IC group, regardless of the baseline risk.

Conclusions. IC reduces the frequency of relapses in ALL children in developing countries, when compared to previous therapy. A highly effective therapy such as m-BFM seems to be the most important predictor of outcome in children. **Med. Pediatr. Oncol. 28:108–116**

Key words: pediatric acute lymphoblastic leukemia; intensive chemotherapy; nonrandomized comparison of therapy

INTRODUCTION

Progress accomplished in the treatment of acute lymphoblastic leukemia (ALL) in children has been remarkable. Standard prognostic factors [1–3] have been used prospectively in multicenter studies applying intensive chemotherapy (IC) [4–10], according to tumor models based on the Goldie-Coldman and Simon hypotheses [11,12]. Considering the improvement in the survival rate achieved by collaborative groups [5,8–10,13,14], we decided to assess the outcome in children younger than 16 years of age who were suffering from ALL and who were treated at our institution. Patients were initially treated with conventional or nonintensive chemotherapy, and later on with the IC regimen used by the Berlin-Frankfurt-Munster group, modified (M-BFM) according to the Gatla-Glahem LLA-84 protocol.

Our study reports the results in 271 children with ALL treated at the National Cancer Institute (NCI) of Bogota, Colombia, the leading referral cancer center in the country, during a 16-year period. We compared two patient groups according to the intensity of chemotherapy and risk factors (age and white blood cell count [WBC]) for relapse present at initial evaluation [15–19]. The primary objective was to compare the efficacy of the two treatment regimens in terms of disease-free survival (DFS) according to the baseline risk. We also wanted to evaluate the feasibility of IC in a developing country setting.

PATIENTS AND METHODS

Patients

One thousand five hundred and thirty nine new cases of malignant disease were diagnosed in children under 16 years of age at the NCI in Bogota between January 1979 and December 1990. Four hundred and sixty six of these new cancer cases were leukemia, 348 (74.7%) of which were ALL. Of the ALL cases, 271 were diagnosed

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Received 6 April 1995; accepted 11 December 1995.

and treated at the NCI; they are the focus of this study. Sixty percent of them came from rural areas. The remaining 77 patients were excluded due to previous treatment outside our institution (59 cases) or because they did not receive all the consecutive phases of the m-BFM protocol (18 children). The diagnosis of ALL in the whole study population was confirmed by bone marrow (BM) aspirate and by the morphological analysis based on the French-American-British (FAB) classification [20]. Cytochemical, cytogenetic, and immunophenotype BM studies could only be performed in 34 patients from the IC group. This small number of cases did not allow us to draw conclusions based on these known prognostic variables.

Treatment

Of the 271 patients of the study population, 141 cases were diagnosed between January 1979 and December 1987; most of these patients received conventional nonintensive chemotherapy (Fig. 1) and formed the historical cohort (HC). The remaining 130 patients were diagnosed between December 1985 and December 1990, and were usually assigned to receive m-BFM therapy without high or intermediate doses of methotrexate (MTX); (Fig. 2). These patients formed the IC cohort. Between 1985 and 1987, patients were treated under either treatment protocol because of family constraints to attend the NCI for intensive treatment. Both therapy groups were classified according to low or high risk for relapse, and the therapy was not modified in relation to these risk factors. The length of treatment in both groups was 36 months [21]. Before 1989, the dose of prophylactic cranial irradiation (PCI) was 24 Gy divided in 2 Gy daily fractions given 5 days per week; after 1989 the dose schedule was modified to 18 Gy in 1.8 Gy daily fractions [22]. The treatment was given through lateral opposite cranial fields with an external megavoltage beam using 6 mV energies or cobalt [23]. Intrathecal chemotherapy (MTX) plus dexamethasone was given five times in weekly intervals during phase 2 of the induction protocol. The dose was age adjusted [24,25], and was postponed only if the platelet count was less than 50×10^9/L.

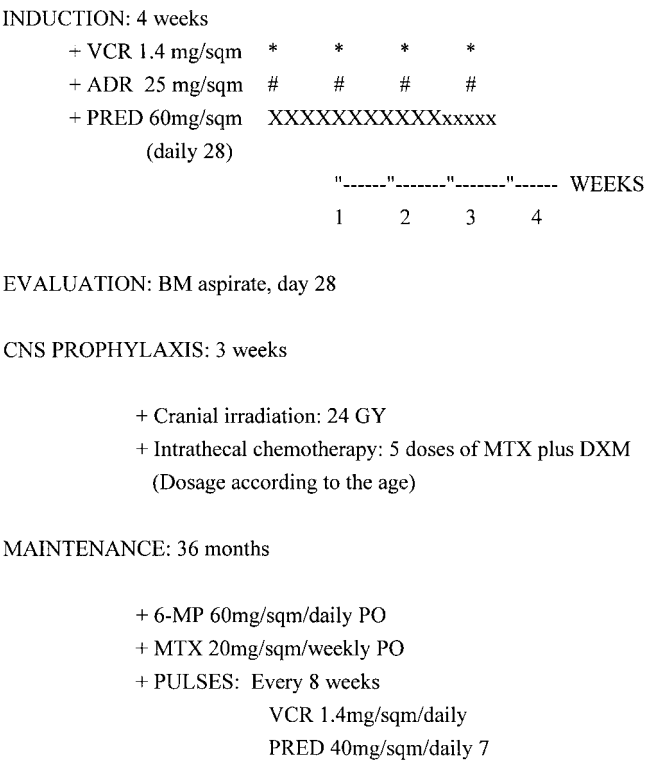

Fig. 1. Conventional or nonintensive therapy protocol used from 1979 to 1987 in the HC group. VCR, vincristine; ADR, Adriamycin, PRED, prednisone; MTX, methotrexate; DXM, dexamethasone; 6-MP, 6-mercaptopurin; BM, bone marrow; CNS, central nervous system.

Follow-Up and Definitions

All children were admitted to the hospital in order to confirm the diagnosis and to begin treatment as soon as possible. Patients showing good response were discharged and continued induction as outpatients. After reaching complete remission (CR), patients in the HC cohort were seen every 2 months during 36 months, while those in the IC cohort were followed every 7–15 days, in order to complete the intensification, reinduction, and reintensification phases. After that period they were seen every 2 months, also until they had completed 36 months of treatment. Since then, all patients visited the NCI every 3 months during 1 year, every 4–6 months for 1 more year, and finally once yearly. Data about CR, relapse, death during remission, treatment failure, and continuous complete remission (CCR) were recorded during the follow-up period. Information concerning clinical features, classification according to risk factors at diagnosis, response to induction chemotherapy, causes of early and late remission deaths, and patterns of relapse and DFS were carefully retrieved from clinical records by one of the researchers (M.T.A.B.). Patients were followed up through July 31, 1995.

Standard risk (SR) was defined as a peripheral WBC of less than 20×10^9/L in patients between the ages of 2 and 10 years at diagnosis. Patients who did not fulfill these criteria or who had evidence of extramedullary disease were classified as high risk (HR). Evidence of extramedullary disease included central nervous system (CNS) involvement with pleocytosis (more than 10 leukocytes/mm^3) and identifiable blast cells in cerebrospinal fluid (CSF) cytology [26], mediastinal widening on chest x-rays, or leukemia-lymphoma syndrome [3]. No manifestations of CNS involvement, such as vomiting, headaches, seizures, or cranial nerve palsies were found on admission. To evaluate the DFS outcome in the group of patients undergoing IC who did not fulfill the SR criteria, these subjects were subdivided into two risk groups as

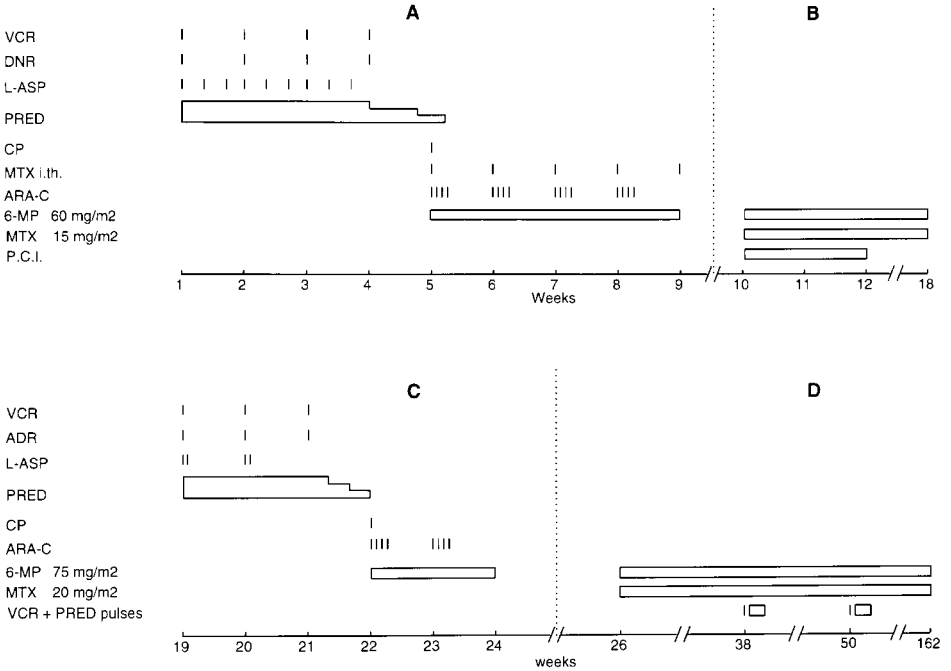

Fig. 2. m-BFM protocol (Gatla-Glahem LLA-84) or IC for ALL therapy used from 1985 to 1990. VCR, vincristine 1.4 mg/m^2 intravenously (i.v.); DNR daunorubicin 25 mg/m^2 i.v., L-ASP, L-asparaginase 6,000 U/m^2 intramuscularly (i.m.); PRED, prednisone 60 mg/m^2 daily, CP, cyclophosphamide 1 g/m^2 i.v., ARA-C, cytosine arabinoside 75 mg/m^2 i.v.; 6-MP, 6-mercaptopurine 60 mg/m^2 daily orally; MTX, methotrexate 20 mg/m^2 once a week orally; ADR, adriamycin 25 mg/m^2 i.v.; VCR + PRED pulses every 12 weeks; MTX i.th, intrathecally age adjusted ($<$1 year 6 mg, 1 to $<$2 years 8 mg, 2 to $<$3 years 10 mg, $\geq$3 years 12 mg). **A:** Modified BFM protocol I; **B:** Short maintenance and PCI; **C:** Modified BFM protocol II; **D:** Long maintenance.

follows: the extremely high-risk (E-HR) group included children with an initial WBC count over 100×10^9/L or who were older than 15 years at diagnosis, while all remaining patients were classified as HR.

CR was defined as the absence of clinical findings related to the disease and a BM aspirate with less than 5% of blast cells on day 28 of treatment. Patients were classified as nonresponsive when no remission was observed after 4 weeks of induction, or when patients with partial remission (5–25% BM blast cells on day 28 of induction) did not experience CR after two additional weeks of chemotherapy. BM relapse was defined as the reappearance of clinical signs related to ALL after CR confirmed by the presence of at least 25% blast cells in the BM aspirate. Testicular relapse was confirmed by histology of ALL on bilateral testicular wedge biopsies obtained at the end of ALL treatment or anytime if the testicular volume was increased. Occult CNS-ALL during follow-up was diagnosed using periodical surveillance of the CSF cytology, performed routinely at 3–6 month intervals. Slides of the CSF sediment were analyzed using Wright's stain and cytomorphology criteria. Samples containing as few as 10 leukocytes/mm^3 but with identifiable lymphoblasts were diagnosed as CNS relapse [26]. Overt CNS leukemia was only seen in 2 out 30 CNS relapses. CCR was defined as no evidence of ALL during treatment or follow-up, with BM, CSF cytology, and testicular biopsy showing absence of malignant cells. Death during remission was established when BM examination at the time of death showed less than 5% blast cells or when autopsy revealed these BM features and no evidence of disease in other organs.

Statistics

The baseline characteristics of the HC and IC groups were compared using Student's t-test for continuous variables and chi-square or Fisher's exact tests for discrete variables. Relative risks (RR) and 95% confidence intervals (95% CI) were obtained for dichotomous outcomes. Survival curves obtained with the Kaplan-Meier method and compared using the log rank test were used to evaluate the statistical association among outcome, type of therapy, and prognostic factors. DFS was measured from the end of induction and excluded 27 patients who died early, 4 who were lost to follow-up during induction, and 33 who did not achieve remission. The events by which DFS was judged were defined as death for any reason, confirmed relapse, or lost to follow-up.

RESULTS

Patient Characteristics

The ALL characteristics at diagnosis and the distribution according to treatment are listed in Table I. Most

TABLE I. Baseline Characteristics of 271 Children With ALL

Patients	HC (%)	IC (%)	*P*
Number	141	130	
Sex			0.93
Male	81 (57.4)	75 (57.7)	
Female	60 (42.6)	55 (42.3)	
Age (years)			0.45
Under 2	5 (3.5)	9 (6.9)	
2–10	94 (66.7)	83 (63.8)	
Over 10	42 (29.8)	38 (29.2)	
Leukocyte count			0.26
Less 20/nl	87 (61.7)	71 (54.6)	
20–99/nl	35 (24.8)	32 (24.6)	
Higher 100/nl	19 (13.5)	27 (20.8)	
Morphology (FAB)			0.28
L 1	112 (79.4)	95 (73.1)	
L 2	29 (20.6)	35 (26.9)	
Extramedullary involvement	17 (12.1)	20 (15.4)	0.54
CNS	10 (7.1)	9 (6.9)	
Mediastinal mass	7 (5.0)	11 (8.5)	
Risk Factor			0.43
Standard	63 (45.4)	51 (39.2)	
High	78 (55.3)	79 (60.8)	

TABLE II. Results of Two Treatment Schedules in 271 Children With ALL

Results	HC (%)	IC (%)	*P*
Patients (n)	141	130	
Death during induction	9 (6,4)	18 (13.8)	0.064
Lost during induction	—	4 (3.0)	
Nonresponse to induction	23 (16.3)	10 (7.6)	0.047
CR	109	98	0.819
Relapses	79 (72.5)	43 (43.9)	0.00005
BM	50 (45.9)	19 (19.4)	0.0001
CNS	14 (12.8)	16 (16.3)	0.6
Testes	7 (6.4)	5 (5.1)	0.9
Combined	8 (7.3)	3 (3.1)	0.289
Death in remission	7 (6.4)	5 (5.1)	0.914
Lost to follow-up	11 (10.1)	7 (7.1)	0.613
CCR	12	43	

patients were male with a 1:1.2 gender ratio. Patients' age ranged from 9 months to 16 years, with 5.2% younger than 2 years, 65.3% between 2 and 10 years, and 29.5% who were older than 10 years. Table I also shows the group distribution based on WBC count, morphological analysis, extramedullary involvement, and risk factor classification. No significant statistical differences were observed in these clinical features. The morphological analysis at diagnosis did not show any case with ALL-L3. However, one patient from the IC group who developed extramedullary involvement 12 months after diagnosis showed B-cell immunological markers at the time of relapse.

Response to Induction Treatment

Twenty-seven children died before completing induction; nine (6.4%) of them were from the HC cohort and 18 (13.8%) were from the IC cohort (RR = 1.58; 95% CI: 1.21 − 2.06; Table II). There were four more cases, all from the IC cohort, who were lost during induction (3.0%). Differences in the mortality rate during the induction phase show borderline statistical significance, even if patients lost to follow-up are considered as survivors ($P = 0.064$). Early deaths in both groups were attributed to complications associated with the disease, such as initial tumor load, which was particularly true for children with more than 100×10^9/L WBC at diagnosis, and complications due to IC, which were primarily seen in the m-BFM group that received four chemotherapy agents simultaneously. Immediate causes of death in both groups included acute bleeding, septic shock, metabolic disturbance secondary to hyperleukocytosis, and less frequently acute pancreatitis found at autopsy and related to L-asparaginase treatment. On the other hand, IC was associated with a lower frequency of failure among those surviving the induction period: only 10 patients (7.6%) treated with m-BFM did not reach CR, compared with 23 (16.3%) in the HC cohort (RR = 0.6; 95%CI: 0.35–1.02; $P = 0.047$).

Occurrence of Relapse

One hundred nine patients (82.6%) of the 132 who survived induction in the HC cohort, and 98 (90.1%) of the 108 known survivors from the IC group were in remission at the end of induction. Eighteen patients, 11 (10.1%) from the HC group and 7 (7.1%) from the IC group, were lost to follow-up after the induction period while they were in CR ($P = 0.613$). The 11 patients lost from the HC group were followed up between 1 and 12 months, while the 7 IC children were followed up from 1 to 21 months. Patients who completed the 36 months of planned therapy and were still free of disease were followed up to 132 months in the HC group (median 67 months) and up to 116 months (median 66 months) in the IC cohort. Table II shows that the frequency of relapses in children who reached CR was greater in the HC cohort (79 of 109 patients, 72.5%) than in the IC group (43 of 98 patients, 43.9%; RR = 0.54; 95%CI: 0.41–0.73; $P = 0.00005$). Table II also indicates that BM was the most common site for relapse, with a proportion greater in the HC group (50 of 79 relapses, 63%) than in the IC group (19 of 43 relapses, 44%; $P = 0.06$). BM relapses were observed in 50 of 109 (45.9%) HC patients who reached CR, and in 19 of 98 (19.4%) IC cases (RR = 0.48; 95%CI: 0.32—0.72; $P = 0.0001$). No differences were found in the frequency of extramedullary relapses between the treatment groups (HC: 21 of 109 = 19.3%; IC: 21 of 98 = 21.4%; $P = 0.83$).

The analysis of the isolated BM relapses according to time of presentation reveals that most of them occurred within the first 18 months in both treatment groups (66% in HC and 68% in IC). CNS relapses were also more

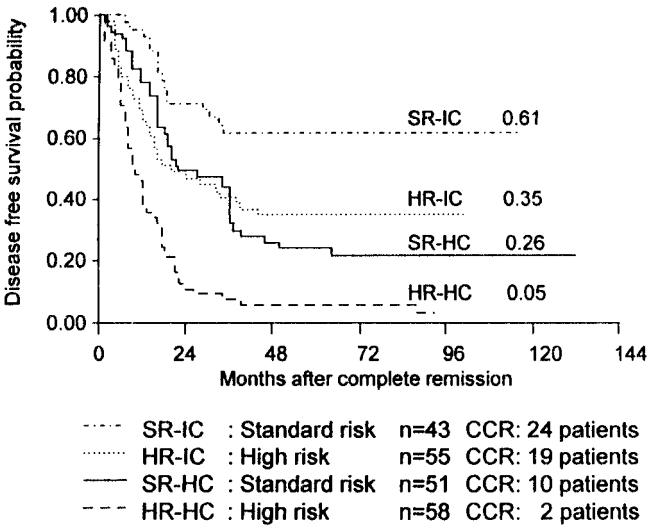

Fig. 3. DFS by treatment and risk. Comparison of DFS between the IC group and the HC group according to baseline risk. SR-IC, standard risk-intensive chemotherapy; HR-IC, high risk-intensive chemotherapy; SR-HC, standard risk-historical controls; HR-HC, high risk-historical controls. SR-IC vs. SR-HC: $P = 0.0007$; HR-IC vs. HR-HC: $P = 0.0001$.

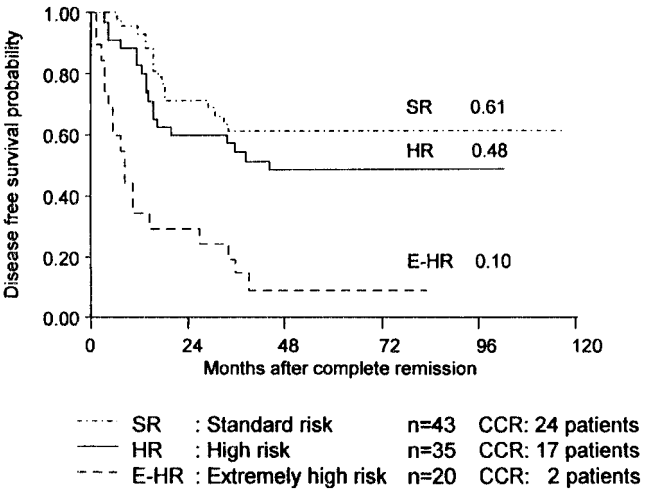

Fig. 4. DFS in the IC group by risk. Comparison of DFS between the IC patients according to baseline risk. SR vs HR: $P = 0.22$; HR vs. E-HR: $P = 0.0002$.

frequently observed in the first 18 months (64% in the HC group and 69% in the IC group). On the other hand, 85% and 80% of testicular relapses were detected 18 months after diagnosis in the HC and the IC groups, respectively. A closer exam of the m-BFM therapy group revealed that 28 of 43 relapses (65%) occurred within the first 18 months after diagnosis, with 13 in the BM, 11 in the CNS, 1 in the testes, and 3 combined.

Patient Outcome Related to Therapy and Risk Factors

Figure 3 shows the DFS in the HC and the IC cohorts in relation to prognostic factors (SR and HR). As expected from our knowledge of the disease biological behavior, DFS was better in both treatment groups for patients classified as SR. Figure 3 also shows that IC treatment produced better results than conventional therapy for both SR ($P = 0.0007$) and HR ($P = 0.0001$) patients. In order to further explore the reasons for the relatively poor results observed in HR children treated with IC (DFS probability 0.35 after 50 months), we stratified these patients into two subgroups according to age and WBC count. The results are shown in Figure 4. No significant differences in DFS were found between SR and HR ($P = 0.22$). However, the E-HR patients had clearly poorer results compared to the other two groups ($P = 0.0002$). Crude relapse rates for SR, HR, and E-HR IC patients were 32%, 49%, and 60%, respectively.

Deaths in CR

There were seven and five deaths in the HC and the IC groups in patients who were in CR, respectively ($P = 0.914$). Four deaths in the HC cohort occurred within 18 months of diagnosis. Autopsy performed in four of the HC fatalities suggested that two deaths were attributable to severe BM hypoplasia with secondary hemorrhage syndrome, one was due to a strongyloides pneumonia, and the fourth was due to diffuse lung alveolar damage, with acute respiratory failure and chronic active hepatitis, all possibly related to chemotherapy. The other three deaths in the HC group were clinically related to bronchopneumonia secondary to varicella and measles (one case each), and to massive pulmonary and CNS hemorrhage associated with BM hypoplasia due to chemotherapy. Four of the IC fatalities were seen within 12 months from diagnosis and the last one after 33 months. The autopsy findings in three IC patients showed two cases of acute hemorrhagic pancreatitis probably associated with L-asparaginase, and one more with severe BM hypoplasia without leukemia infiltration. The other two fatal cases were clinically related to infection and sepsis during intensification therapy in one child, and with varicella and acute respiratory failure during the maintenance phase in the other.

Late Toxicity

Neuropsychological and cognitive impairment have not been investigated in detail in this population. In general, our ALL patients seem to have more learning disabilities and lower academic achievement than normal children of similar age. One case of thyroid papillary carcinoma was found after 41 months of ALL diagnosis in the IC group; no second malignant CNS neoplasms have been found among survivors up to date. Finally, four females (three from the IC group and one from the HC cohort) and one male (from the IC group) have had normal offspring.

DISCUSSION

This study aimed to compare the efficacy of IC in children with ALL seen at the NCI in Bogota, Colombia, as compared with that observed with conventional treatment. In general, our results show that the m-BFM protocol produces better results than conventional therapy, as suggested by a clinically important (46%) reduction in the risk of relapse (Table II) as well as by significant differences in DFS (Fig. 3). We consider it an important achievement that one IC protocol for children's ALL, such as m-BFM, could have been successfully implemented in a reference cancer center in a Third World country. This was due to extensive cooperation among patients, their families, and the pediatric oncology unit team (social workers, nurses, and physicians).

Our study used HCs to compare the results of two cohorts of children with ALL treated with different therapies at different time periods. Prospective randomized studies are the ideal design for evaluating the effectiveness of different therapy protocols [27,28]. However, both practical and methodological circumstances at our institution precluded us to conduct a large study with concurrent controls. Although the NCI is the national referral center for cancer, it can be difficult to identify large numbers of patients to conduct a study with simultaneous controls within a reasonable period of time in just one center. As mentioned before, there was a period in which patients were treated with either regimen, due to logistic and financial constraints. Finally, randomized trials are more expensive and logistically difficult for us.

Even though we recognize that the use of HCs can produce biased results for several reasons, we believe that our study has some strengths. Baseline differences between IC patients and HCs could explain part of the differences observed in the outcomes. However, the HC and IC groups had similar distributions in factors such as gender, age, morphological type, and risk classification (Table I), which suggest that they were comparable in several well-recognized prognostic factors. Unfortunately, some biological features that are important predictors could not be estimated in this study. These include the presence of early pre-B calla negative immunophenotype [3,4] and cytogenetic abnormalities such as 4;11 and 9;22 translocations [1,29], which are associated with a worse prognosis independent of WBC [30], the simultaneous antigen expression of myeloid and lymphoid lineage [31], and the effects of the HTLV-1 retrovirus associated with the leukemia adult T-cell lymphoma syndrome, which has a high prevalence in the Caribbean basin to which our country belongs [32]. It is also possible that the use of new or improved management strategies for complications explains part of the increase in survival observed along the study period. Although we recognize that these changes in the supportive management may have contributed to the differences in survival between the treatment groups, it is unlikely that they are the only reason for the important reduction in the risk of relapse observed in our ALL patients. Finally, all patients were diagnosed, treated, and followed up by the same team who used standard diagnostic criteria and very similar follow-up mechanisms for all patients, with rigorous attention to the treatment schedule. Thus, changes in these factors are not a feasible explanation for the differences found in our study. Despite all these limitations, we believe that in our circumstances this retrospective study can produce useful and valid results [33].

Our results suggest that the rate of remission during induction was slightly better (91%) in the m-BFM group, which simultaneously received four agents, than in the HC group (83%); however, this difference was not statistically significant. On the other hand, it is necessary to point out some limitations in the application of IC in a Third World country. The induction regimen of IC with four drugs increased early mortality (Table II), probably due to drug toxicity, limited supportive measures, adverse socioeconomic conditions, and large geographical distances. We believe that a program of gradual induction could produce less toxic effects, allowing time for improving the patients' general condition, already deteriorated by the ALL burden, associated infections, and hemorrhage. It could also permit the evaluation of the peripheral blast cell count response to prednisone therapy, providing useful prognostic information for survival [34,35]. On the other hand, the neutropenic fever episodes observed in two of every three patients receiving IC during weeks 5–9 and again during weeks 19–24 lead us to postpone some doses of chemotherapy (therefore extending its total duration), which could have reduced the treatment final effectiveness. The challenge then is to identify minor modifications in the BFM therapy that could improve its safety without reducing its long-term usefulness. If this can be accomplished in the near future, our overall results will improve. We are aware that these initial difficulties decreased as our experience in the IC management increased.

Despite the higher early mortality and some unplanned modifications in the length of therapy mentioned above, it is clear that relapses were significantly less common in the IC group when compared to the HC group (43.9% and 72.4%). This represents an absolute RR reduction of 46%. Almost all this improvement is due to a reduction in the frequency of BM relapses, observed in 19.3% and 45.8% of IC and HC patients, respectively. With better control of medullary disease, meningeal leukemia appears to be the major obstacle in the cure of our ALL patients [36,37]. We found a slightly higher rate of meningeal relapses in the IC group (16.3%) when compared to the HC group (12.8%), results that are worse than the 10% reported in the literature [37]. A disturbing result was

that 5 of 16 relapses in the m-BFM group were seen in SR patients who got 18 Gy as PCI, a finding that has also been reported in other studies [13]. The high incidence of CNS relapses made it necessary to consider in detail some issues related to PCI planning and delivery. Although the prescribed dose was standardized, it was not delivered using a fixed technique protocol because sequential verification films were not obtained, and because simulation or computed tomographic (CT)-exams were not available before 1990. Besides, the safety margins for reliable coverage of critical CNS areas were based only on osseous reference marks, which can produce a higher incidence of CNS relapses due to the considerable anatomical variation in children younger than 12 years of age [38]. Finally, sedation and fixation with face masks were not available for all patients. All these factors have been shown to be very important in prescribing PCI [38], because any area of significant underdosage may increase the chance of relapse [39,40]. Finally, the finding of meningeal leukemia strongly suggests the presence of hidden blast cells in other sites, or that the patient has severe, extensive, or biologically aggressive ALL [36]. Seven percent of our patient population had meningeal leukemia at diagnosis, a frequency slightly higher than the 4% reported in the literature [4].

The identifiable prognostic factors used in our study are based on information about how age and leukocyte count representing tumor volume affect the response to therapy [15,16]. These factors have useful clinical applications but they are based on somewhat empirical and arbitrary criteria [14,41]. The Kaplan-Meier survival curves that compare DFS in both treatment schedules (Fig. 3) clearly show a better therapeutic result for m-BFM in both SR ($P = 0.0007$) and HR patients ($P = 0.0001$). Although the comparison between both risk groups treated with m-BFM (Fig. 3) shows a clear statistical difference ($P = 0.0045$), we were disappointed with the poor results for HR-IC patients. This motivated us to redefine the risk of relapse and further divide these HR patients into two groups as shown in Figure 4. The E-HR represented 20% of the ALL cases treated with m-BFM, and they clearly had an adverse outcome. Thus, it is possible that these patients could represent a group of ALL with different biological behavior. We believe this group of E-HR ALL patients requires a more intensive chemotherapy schedule [42] with better supportive measures, which could include the use of growth factors. We also believe that these HR children are a group that deserves a more precise redefinition based on initial cytogenetic findings, response to prednisone on day 8 and immunophenotype. As far as for the remaining 80% of children is concerned, another interesting aspect of this study was that the usual risk categories based on age and WBC did not predict very well the long-term follow-up results, suggesting that these variables lost part of their significance as prognostic factors. We did not find statistical significant differences at 8 years of follow-up between SR children and those considered as HR patients treated with the same m-BFM chemotherapy schedule ($P = 0.22$; Fig. 4). This confirms what has been previously reported by others [5,13,34], that a highly effective therapy is one of the most important prognostic factors in childhood ALL. Despite the fact that we could not apply the morphological, immunological, and cytogenetic (MIC) classification [43] in this study, we did confirm that childhood ALL is a life-threatening condition that requires early and adequate management [1,5,14]. Finally, it is very important that ALL patients have a long-term follow-up because short-term results may give a false impression about the true behavior of the disease [44]. This had been confirmed by our own experience, because our preliminary results are different from those reported here [45].

An effective strategy to obtain better control of ALL could be the addition of high doses of agents with good CNS penetration [37,46], early prophylactic intrathecal chemotherapy, and the addition of dexamethasone during the induction phase [47–49]. Our DFS results and the incidence of CNS relapses led us to use 24-hour infusions of high doses of MTX [50,51] along with intrathecal triple-agent therapy, using MTX, cytosine arabinoside, and dexamethasone [48]. We hope that this approach will contribute to a better control of extramedullary leukemia, and to a reduction of the endocrine and neurological dysfunction associated with CNS prophylactic radiation therapy, especially in children defined as having strictly SR ALL. This issue has been previously discussed in the preliminary studies of BFM therapy and in other protocols of ALL [9,36,46,48,52]. We are already collecting data that will allow us to compare the effectiveness of this form of treatment with those reported in this study.

Finally, we believe our results are comparable to those reported by several groups that have studied IC in childhood ALL in developing countries. The feasibility of this form of treatment has also been demonstrated by the preliminary findings of the Arabian and the Brazilian groups [53,54]. Remarkably poor event-free survival results with nonintensive treatment were reported by the Turkish group, also using HCs [55]. The studies conducted in Chile [56] and Spain [57] showed low event-free survival rates for children with very high risk for relapse despite BFM therapy, findings that are very similar to those reported here. Finally, the Argentinean group showed the remarkable importance of delayed intensification for patients with high risk for relapse [58]. On the other hand, our study had a larger number of patients than two of these studies [53,54], and included a larger proportion of E-HR patients (20%), when compared with 12% in the Chilean study and 10% in the Spanish report [56,57].

In conclusion, our study confirms that it is possible to

deliver IC to children with ALL living in developing countries. The results show that this form of treatment produces a higher rate of CR, reduces the risk of relapses, mainly at the BM level, and produces better DFS rates at 10 years of follow-up, regardless of the baseline risk. However, it did not reduce the frequency of CNS relapses and produced a higher mortality during induction. These findings suggest that the intensity of chemotherapy is an essential factor that can determine the success or failure of treatment [3,5,34,44]. The effort required for IC for ALL is warranted because we have the responsibility to offer the best treatment to children with this condition, a disease with a high rate of cure [1,2,9,10,34]. This justification is even greater in developing countries, where the scarceness of resources makes it difficult to deliver second-line chemotherapy rescue or to perform bone marrow transplantation in patients who relapse following less intensive treatment [3,4,34]. This protocol offers SR and HR ALL children a good opportunity for cure as confirmed with nearly a decade of follow-up.

ACKNOWLEDGMENTS

We thank Helmut Gadner, MD, St. Anna Children's Hospital, Vienna, for his help in understanding and applying BFM therapy and in preparing this manuscript. We also thank Gunther Henze, MD, Department of Pediatrics, Free University of Berlin, for his helpful comments.

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